Clinical Outcomes of Endoscopic Submucosal Tunnel Dissection Vs Endoscopic Submucosal Dissection in Gastric Lesions: a Systematic Review and Meta-analysis

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Research Article

Keywords: Endoscopic submucosal tunnel dissection (ESTD), endoscopic submucosal dissection (ESD), early gastric cancer, gastric precancerous lesions, meta-analysis

Posted Date: June 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-545069/v1

Abstract

Background and objectives: Many studies have verified that endoscopic submucosal dissection (ESD) has prominent advantages in *en bloc* resection and low recurrence rate. However, ESD also has technical difficulty for some large-area gastric lesions. Endoscopic submucosal tunneling dissection (ESTD) combined the tunnel technique with the traditional ESD technique for treating gastrointestinal mucosal lesions under tunnel endoscopy. This technique has been gradually applied to the treatment of large-scale early cancer and precancerous lesions, and has achieved good results. Yet no meta-analysis has been published, so we performed this study to determine the efficacy and safety of ESTD vs ESD in gastric lesions through clinical outcomes.

Methods: We performed the literature search in PubMed, Cochrane Library, Web of Science, Embase, Wanfang, and CNKI dating up to February 9, 2021. Studies comparing the clinical outcomes of ESTD and ESD in gastric lesions were enrolled. The Newcastle-Ottawa Quality Assessment Scale was used to evaluate the quality of these studies.

Results: Four articles were included that involved a total of 920 patients (187 from the ESTD group and 733 from ESD group). ESTD has higher *en bloc* resection and R0 resection rate, faster dissection speed, and lower complication rate. The curative resection rate and recurrence rate of ESTD group is comparable with ESD group.

Conclusions: ESTD technique is an effective and safe treatment procedure in gastric lesions, and may be prior to ESD for large gastric lesions.

Introduction

With the development of endoscopic technology, the detection rate of gastrointestinal lesions (including early cancer) has been significantly increased (1, 2). Endoscopic resection has been recommended as a first-line treatment for some patients. Available methods include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), radiofrequency ablation (RFA), etc.(3, 4).

Endoscopic submucosal dissection (ESD) was firstly described in 1988 as a technique for the treatment of early gastric cancer(5). Since 2004, ESD has been widely accepted as a new method, which allows single-piece resection, so as to obtain good histological results(6). ESD has prominent advantages in *en bloc* resection and low recurrence rate, compared with EMR and RFA. However, technical difficulty encounters when performing ESD for some large-area gastric lesions. The main problems are as following: 1) the effect of submucosal injection after circumferential incision is relatively poor; 2) when gradually peeling off to the middle, the surrounding lesion mucosa retracts, making the operation vision unclear.; 3) sometimes, elevation of the submucosa is difficult.

To overcome these difficulties, in 2011, professor Linghu Enqiang(7) combined the tunnel technique with the traditional ESD technique, and improved and proposed a technique for treating gastrointestinal mucosal lesions under tunnel endoscopy, and named it endoscopic submucosal tunneling dissection (ESTD). This technique has been gradually applied to the treatment of large-scale early cancer and precancerous lesions, and has achieved good results. This technology was first applied to the endoscopic treatment for large-area early esophageal cancer. Many studies have showed that it was superior to traditional ESD in efficacy and safety. The study of Cecile(8) verified the safety of ESTD on a pig animal model. The studies of Gong(9) and Ken(10) respectively summarized 55 and 11 patients who underwent ESTD treatment for large-area early cancer of the esophagus, verifying the efficacy and safety of ESTD. The study of Tang(11) summarized the use of ESTD in digestive tract tumor, which further verified the safety of ESTD. In theory, compared with traditional ESD, ESTD has the following advantages: 1) A clearer vision was provided through countertraction of bilateral stretching mucosa for operation and prevents mucosa from retraction, which facilitates dissection and reduces the risk of complication. 2) The amount and time of injection can be reduced by directly injecting and retaining submucosal solutions in the submucosal layer. 3) An easier dissection close to the MP layer and complete resection of the submucosal layer providing a better histologically resected specimen and facilitates the dissection of lesion with ulcer or fibrosis. 4) The transparent cap contributes to blunt dissection in the tunnel(3, 12, 13).

Many studies have verified the efficacy and safety of ESTD in gastric lesions, however, no meta-analysis has been published. Therefore, we performed this study to determine the efficacy and safety of ESTD vs ESD in gastric lesions through clinical outcomes.

Methods

Systematic review registration number

Our systematic review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/prospero/, registration number: CRD42020179779)

Definition

En bloc resection was defined as a one-piece resection of the entire lesion as observed endoscopically(14). R0 resection was defined the lesion was removed as one piece with pathologically negative margins(15). Curative resection was achieved when both the lateral and vertical margins of the specimen were free of cancer and there was no invasion deeper than 1000 μm from the muscularis mucosae, lymphatic invasion, vascular involvement, or poorly differentiated component(16). The dissection speed (mm^2/min) was defined as the specimen area (mm^2) divided by duration (min). Recurrence was defined as the lesion detected in the follow-up after surgery. Complications include muscular injury, perforation, intraoperative and postoperative bleeding.

Literature search

Jianglei Li and Yuyong Tan performed the literature search and data extraction. PubMed, Cochrane Library, Web of Science, Embase, Wanfang and CNKI databases were searched, including all entries from the inception of the database up to and including 9 February 2021. The following search terms were used: ‘endoscopic submucosal tunnel dissection’, ‘ESTD’, ‘endoscopic submucosal dissection’, ‘ESD’, ‘stomach’ and ‘gastric’. We searched free terms as well as MeSH words, and we reviewed the references of all retrieved studies to identify any other relevant literature.

Electronic search strategy for PubMed: ((endoscopic submucosal tunnel dissection) OR ESTD) AND ((endoscopic submucosal dissection) OR ESD) AND ((stomach) OR (gastric))

Study selection

Studies meeting the following criteria were included: (a) studies involving patients diagnosed with gastric lesions and treated with ESTD or ESD, (b) studies conducted to compare ESTD and ESD in gastric lesions, and (c) studies reporting clinical outcomes after ESTD or ESD, including *en bloc* resection rate, R0 resection rate, curative resection, specimen area, operation time, dissection speed, complications and recurrence. The exclusion criteria were: (a) case reports, reviews, or conference abstracts, (b) studies lack of sufficient data.

Data extraction and quality evaluation

The titles and abstracts of articles were screened independently by two reviewers and the following information was extracted: author names, study design, publication year, study period, region, number of patients, baseline characteristics of patients, clinical outcome data including *en bloc* resection rate, R0 resection rate, curative resection rate,complications, operation time, dissection speed and recurrence rate. Study quality was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS); studies with NOS scores of more than six points were considered high-quality articles.

Statistical analysis

A fixed-effects model was used for data analysis, except when data were considered significantly heterogeneous. In that case, a random-effects model was used. We chose odds ratios (ORs) to evaluate differences in *en bloc* resection rate, R0 resection

rate and curative resection rate between the ESTD and ESD groups. And we chose weighted mean differences (WMDs) for specimen area, operation time and dissection speed. P values less than 0.05 were considered significant. Statistical heterogeneity was assessed using Q^2 tests and Higgins I^2 statistics. Values of $P < 0.10$ or $I^2 > 50\%$ indicated statistical significance. In case of statistically insignificant heterogeneity, a fixed-effects model was adopted. Otherwise, a random-effects model was applied. All statistical analyses were performed using Stata 14 (Stata Corp., College Station, Texas, USA). Begg's test was performed to assess publication bias on the *en bloc* resection rate.

Results

A total of 459 articles were retrieved in the literature search and 4 of them met the selection criteria (Fig. 1). These studies involved a total of 920 patients (187 from the ESTD group and 733 from the ESD group). The baseline characteristics and quality assessments of the studies are shown in Table 1(17–20). Four studies retrospectively analyzed patients who were diagnosed with gastric lesions and treated with ESTD, and collected patients who underwent ESD treatment during the same period to analyze their clinical indicators and prognosis. Ojima's study(20) was a matched study, but because the other three studies were not matched, we included data from unmatched patients. Ojima's study did not give the average value on specimen area, operation time and dissection speed. We obtained the average value(21)and standard deviation(22) through the method of conversion.

Table 1
Baseline characteristics and quality assessment

Research	Study design	Enrollment period (year)	Region	Patients number		Age, years		Gender (M/F)		NOS
				ESTD	ESD	ESTD	ESD	ESTD	ESD	
Li, 2015 (14)	retrospective	2012.1-2012.12	Tianjin, China	7	13	63.3	66.4	6/1	10/3	7
Feng, 2018 (15)	retrospective	2012.1-2014.1	Beijing, China	7	7	63.3	61.1	6/1	4/3	7
Zhang*, 2018 (16)	prospective	2014.6-2016.6	Suzhou, China	32	55	64.0		48/39		7
Ojima, 2020 (17)	prospective	2015.1-2018.6	Wakayama, Japan	141	658	72(49–93)	72(30–94)	99/42	479/179	7
*: Information on age and gender was not given separately										

En bloc resection

Regarding the *en bloc* resection rate, the results revealed significantly higher *en bloc* resection rate in the ESTD group than in the ESD group (pooled OR: 107.20, 95% CI: 24.90 to 461.43, P = 0.000; Fig. 2). No obvious heterogeneity was found ($I^2 = 22.4\%$, P = 0.276).

R0 resection

The R0 resection rate was significantly higher in the ESTD group than in the ESD group (pooled OR: 2.329, 95% CI: 1.064 to 5.098, P = 0.034; Fig. 3). No obvious heterogeneity was found ($I^2 = 0.0\%$, P = 0.635).

Curative resection

The curative resection rate was not significantly different between two groups (pooled OR: 1.563, 95% CI: 0.934 to 2.616, P = 0.089; Fig. 4). No obvious heterogeneity was found (I^2 = 0.0%, P = 0.469).

Specimen area, operation time and dissection speed

The specimen area was significantly larger in the ESTD group than in the ESD group (pooled WMD: 2.774, 95% CI: 0.666 to 4.882, P = 0.010; Fig. 5). Significant heterogeneity was detected (I^2 = 95.4%, P = 0.000), and a random-effects model was used. The operation time was not significantly different between the patients who underwent ESTD and those who underwent ESD (pooled WMD: -23.434, 95% CI: -50.575 to 3.706, P = 0.091; Fig. 6). Significant heterogeneity was detected (I^2 = 82.8%, P = 0.001), and a random-effects model was used. Regarding the dissection speed, the results revealed significantly faster in the ESTD group than in the ESD group (pooled WMD: 5.913, 95% CI: 0.207 to 11.618, P = 0.000; Fig. 7). Significant heterogeneity was detected (I^2 = 90.1%, P = 0.000), and a random-effects model was used.

Complications

The complication rate was significantly lower in the ESTD group than in the ESD group (pooled OR: 0.209, 95% CI: 0.097 to 0.451, P = 0.000; Fig. 8). No significant heterogeneity was detected (I^2 =43.3%, P = 0.152).

Recurrence

In this comparison, the ESTD group had no significantly lower recurrence rate after operation than the ESD group (pooled OR: 0.714, 95% CI: 0.171 to 2.977, P = 0.644; Fig. 9). No significant heterogeneity was detected (I^2 =0.0%, P = 0.985).

Publication bias

Begg's test was performed for publication bias based on *en bloc* resection rate. No publication bias was observed in these analyses (Fig. 10, P = 0.308).

Discussion

A high *en bloc* resection rate is one of the most important influence for choosing management a way for malignant of potentially malignant lesions and R0 resection is an important parameter related to further treatment and recurrence which should be considered as a judgment standard in choosing therapies(23). The result of our study showed that these two indicators in the ESTD group were significantly higher than those in the ESD group. Due to the narrow range of operation, ESD has a poor endoscopic display effect in gastric which lead to the difficulties of *en bloc* resection and R0 resection. Compared with ESD, ESTD establishes submucosal tunnel during surgery, which improves the full exposure of surgical field and the clarity of submucosal blood vessels and tissues(24). As a result, these advantages maybe make surgical operation more convenient and increase the overall resection rate and R0 resection rate.

For an operation, operation time and dissection speed are the vital success factors. For example, the less time of surgery can decrease the likelihood of complications such as bleeding, anesthesia-related adverse events (12) and the fast dissection speed probably represents the accuracy and efficiency of the surgical technique. Since the four studies are all retrospective studies, grouping is not a double-blind method, and there are significant differences in the specimen area between the two groups. Therefore, although there is no significant difference in operation time, the speed of resection ESTD is significantly higher than that of ESD. On the one hand, as previously mentioned, ESTD provided a better view and operation space which reduced the difficulty of operation. On the other hand, ESTD can use the transparent cap at the front end of the gastroscope which is in the tunnel to inject CO_2 to enable blunt submucosal separation. As a result, the dissection time will be significantly decreased and the dissection speed will be improved(25).

ESD and ESTD both have complications such as muscular injury, perforation, intraoperative and postoperative bleeding. As we all known, complications have great influence on life quality and recovery of patients. It will not only aggravating the pain to

the patient, but also caused economic burden for cure to the family and society furthermore. According to this situation, reducing the happening of adverse events has a significant meaning for the material life and mental state of the patients. In this study, we found that the rate of these events in the ESTD group is lower than ESD group. As for the reason, we think that ESTD can not only increase the efficiency of the surgery to reduce the chances of complications, but also reduce damage to blood vessels and muscularis by the establishment of the tunnel. The result showed us that the ESTD has more benefits to prognostic than ESD in the operation of excising gastric lesions.

There were several limitations in our meta-analysis. First, our enrolled articles only have four retrospective studies including, and all of them were came from Asia which maybe cause the influence to the results because of the race, environment or other factors. And according to the difference of diagnostic criteria, morbidity and treatment guidelines, we need larger randomized controlled trials or high-quality comparative studies to obtain more reliable and general data to analysis the difference between ESD and ESTD. Secondly, the studies of operation time, dissection speed and complications have an obvious clinical heterogeneity. For the operation time and dissection speed, the heterogeneity may be caused by several reasons including the different operational proficiency of the surgeon, the varieties of the degree of advanced equipment and the different size of lesion area of patients. And as the heterogeneity of the complications, when excluding these data of this article the heterogeneity is lower than before. This result mentioned us that different source of data, inclusion criteria, research method or kinds of complications may lead to the heterogeneity.

A recent meta-analysis (26) compared the superiority of ESTD and ESD in treating superficial upper gastrointestinal superficial precancerous lesions and tumors. However, as for comparing the difference treatment of gastric lesions, only two studies including a total of 101 patients (39 from ESTD group and 62 from ESD group) were enrolled. We collected the data of 4 studies including 920 patients (187 from ESTD group and 733 from ESD group). Our meta-analysis further demonstrated the efficacy and safety of ESTD and revealed the potential advantages of ESTD as an ESD.

In summary, our meta-analysis suggests that ESTD has more advantages in treating the gastric lesions than ESD, such as *en bloc* resection rate, R0 resection rate, dissection speed and complications. And further long-term and follow-up prospective randomized controlled trials need to be done on a large scale to collect more patients' data, especially in western countries, for analysis of advantages and disadvantages.

Declarations

Authors' contributions

Jianglei Li acquired data, performed analysis, interpreted the data, and drafted the manuscript. Yuyong Tan acquired data, performed analysis, and interpreted the data. Mengmeng Xu interpreted the data and revised the manuscript. Yongjun Wang interpreted the data and revised the manuscript. Deliang Liu made critical revisions to the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to give our sincere gratitude to Dr. Lesan Wang for his support for statistical analysis.

Conflict of interest

Authors declare no Conflict of Interests for this article.

Ethics approval and consent to participate

N/A

Consent for publication

Jianglei Li , Mengmeng Xu , Yuyong Tan , Yongjun Wang and Deliang Liu are all constent for publication.

Availability of data and materials

The data-sets used and/or analysed during the current study available from the corresponding author on reasonable request.

Funding

Not applicable.

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Figures

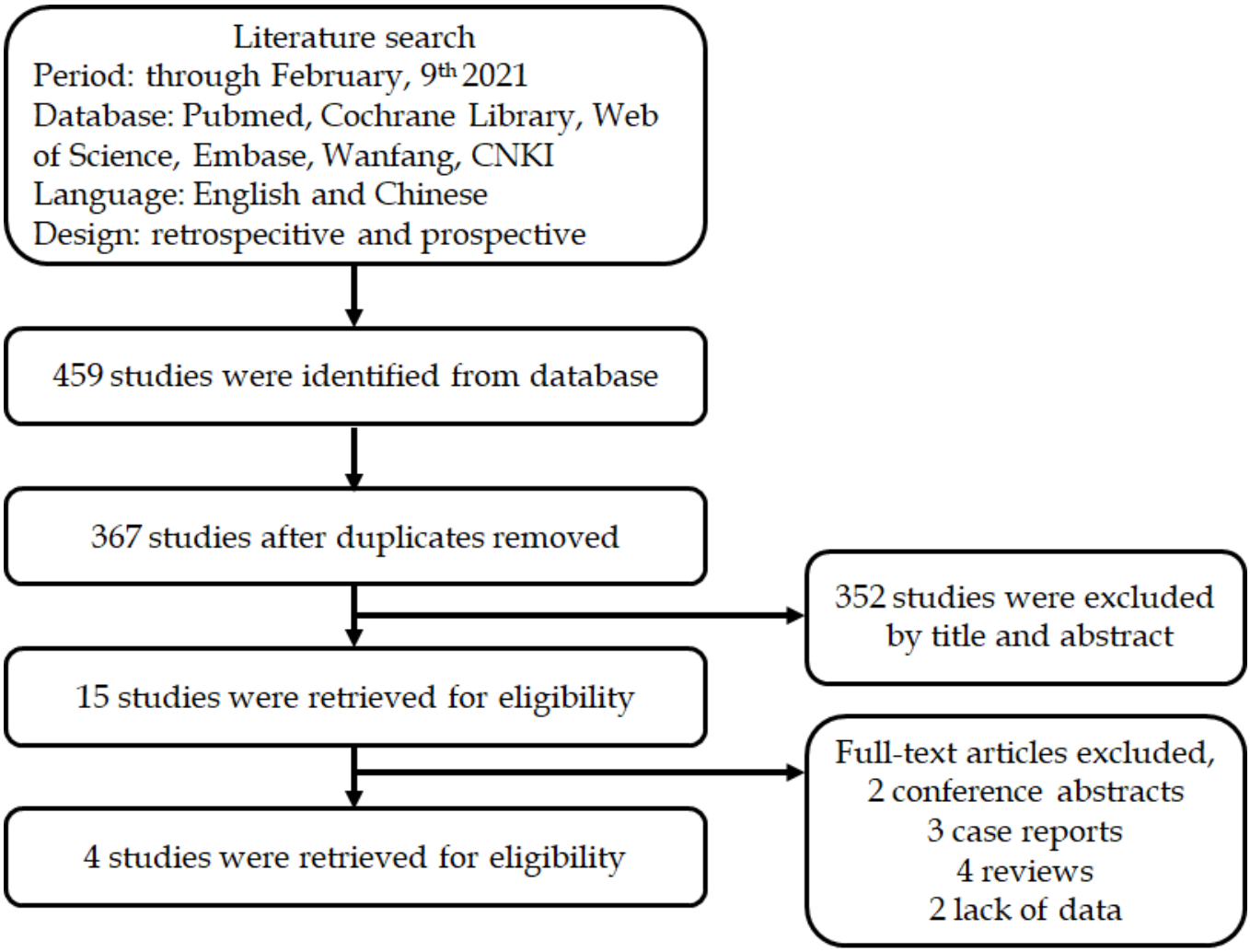

Figure 1

Flow chart of study enrollment.

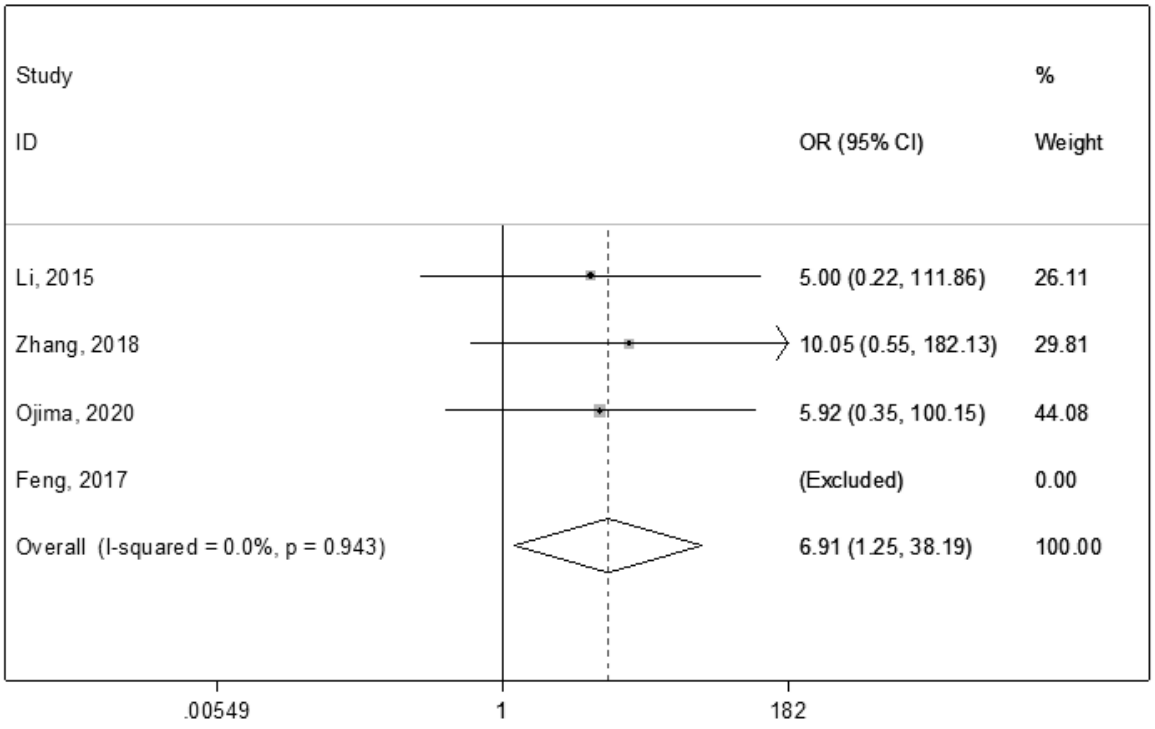

Figure 2

Comparison of en bloc resection rate for ESTD vs. ESD in gastric lesions.

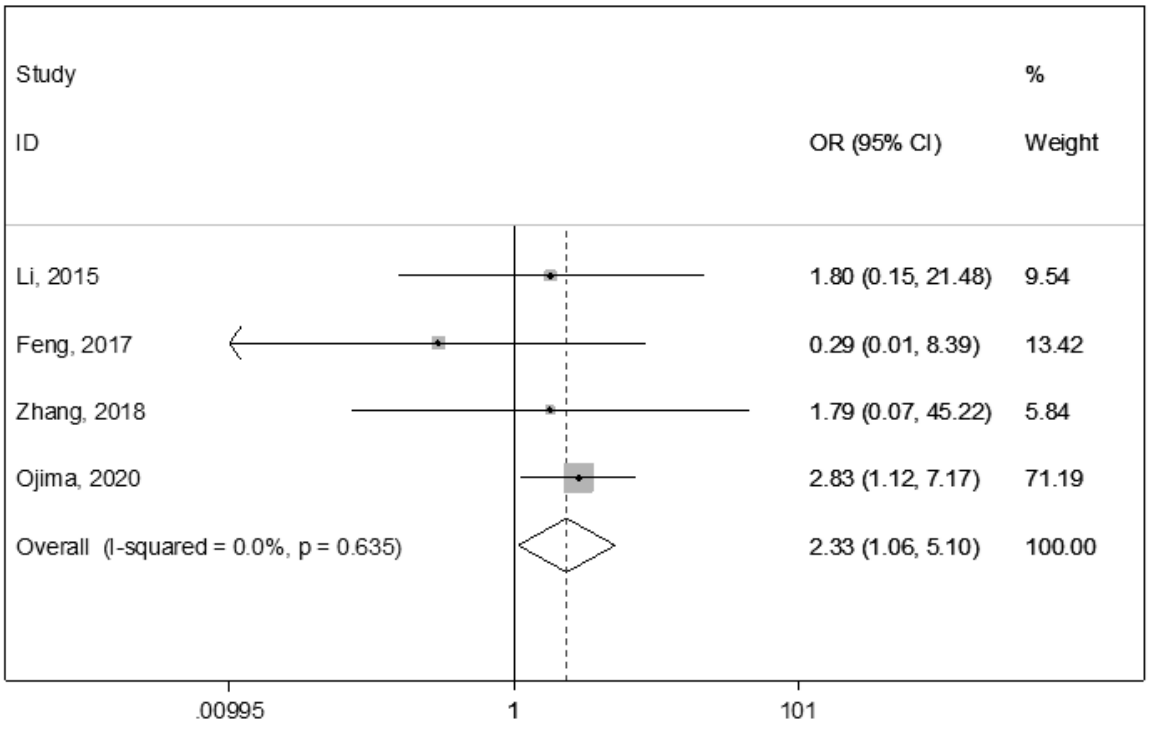

Figure 3

Comparison of R0 resection rate for ESTD vs. ESD in gastric lesions.

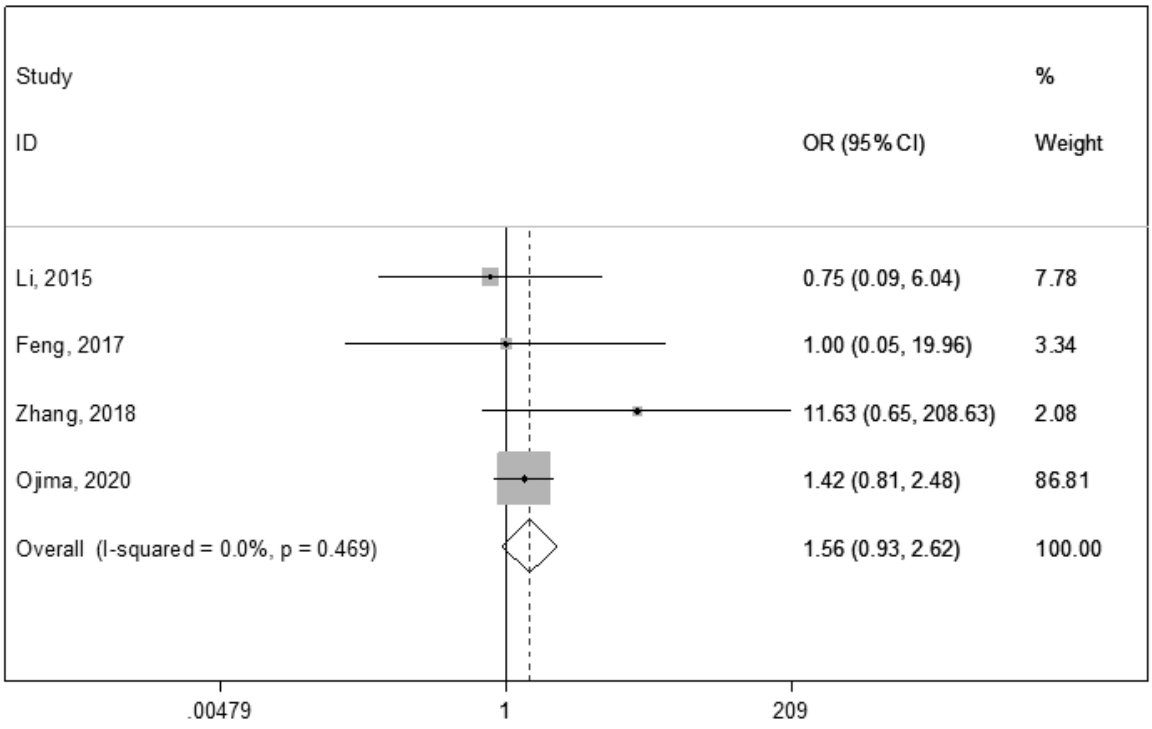

Figure 4

Comparison of curative resection rate for ESTD vs. ESD in gastric lesions.

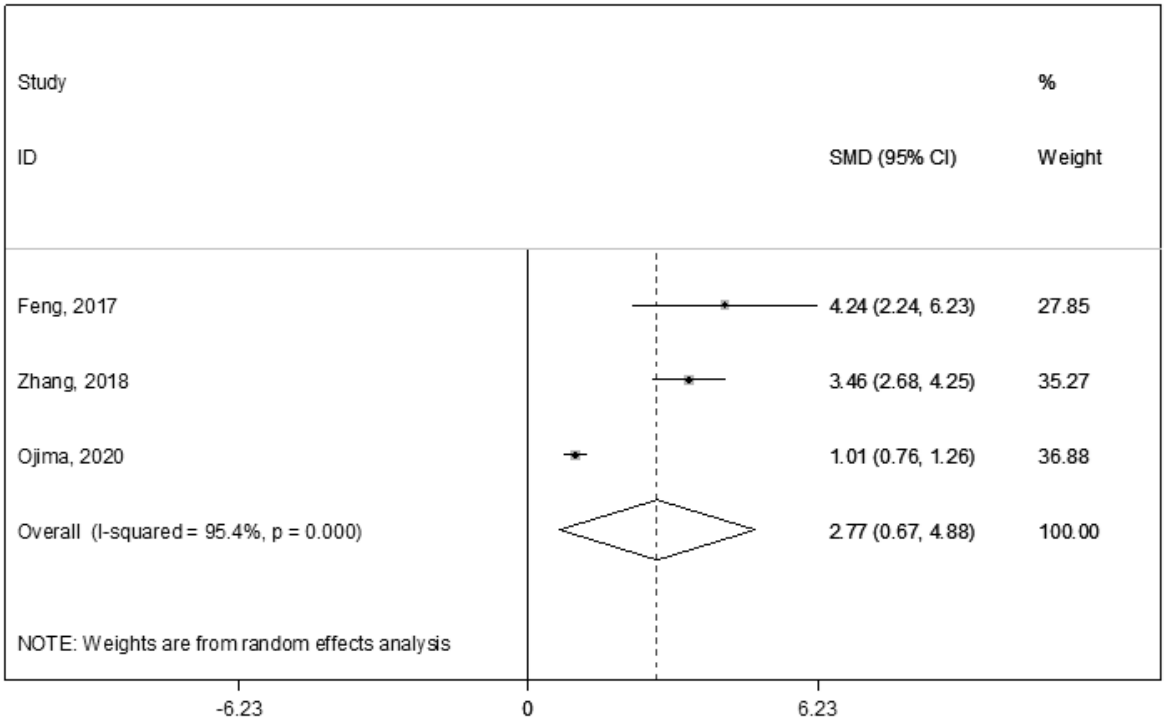

Figure 5

Comparison of specimen area for ESTD vs. ESD in gastric lesions.

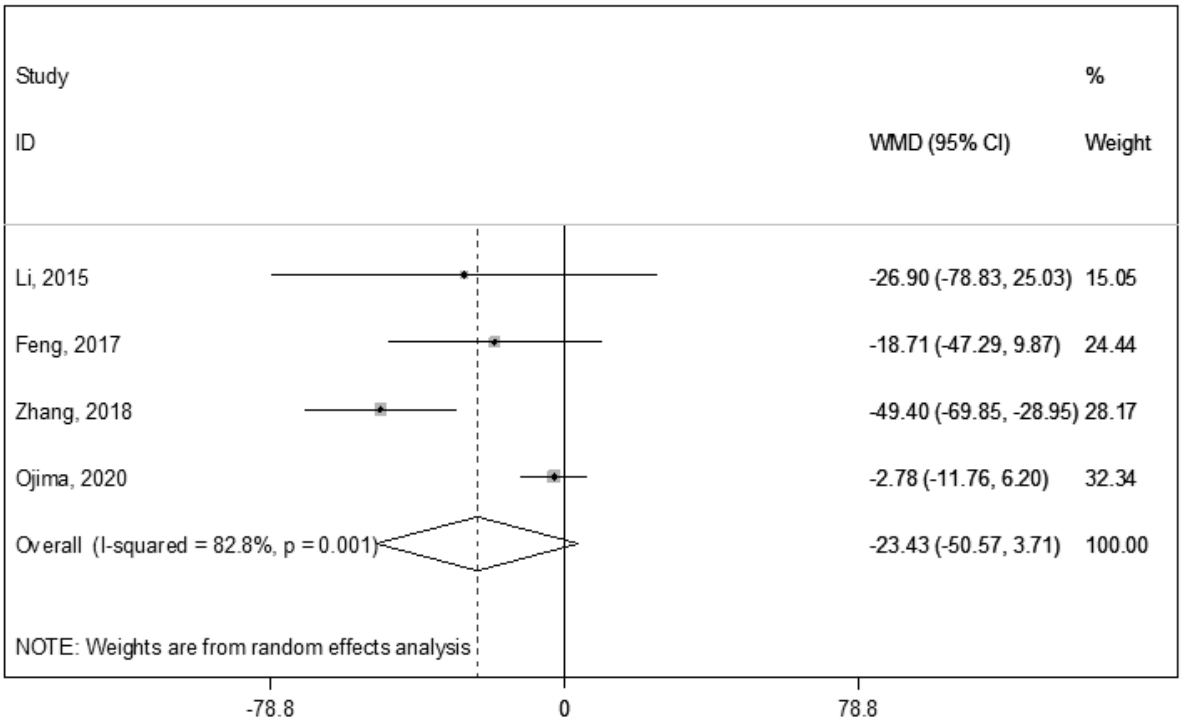

Figure 6

Comparison of operation time for ESTD vs. ESD in gastric lesions.

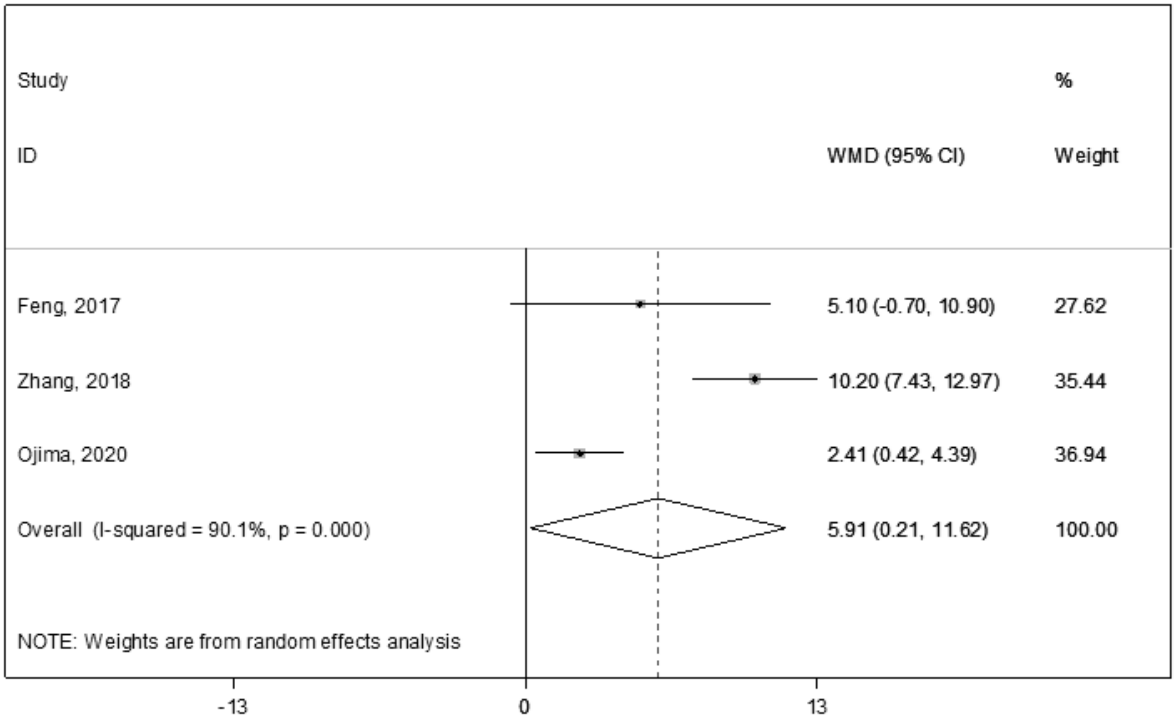

Figure 7

Comparison of dissection speed for ESTD vs. ESD in gastric lesions.

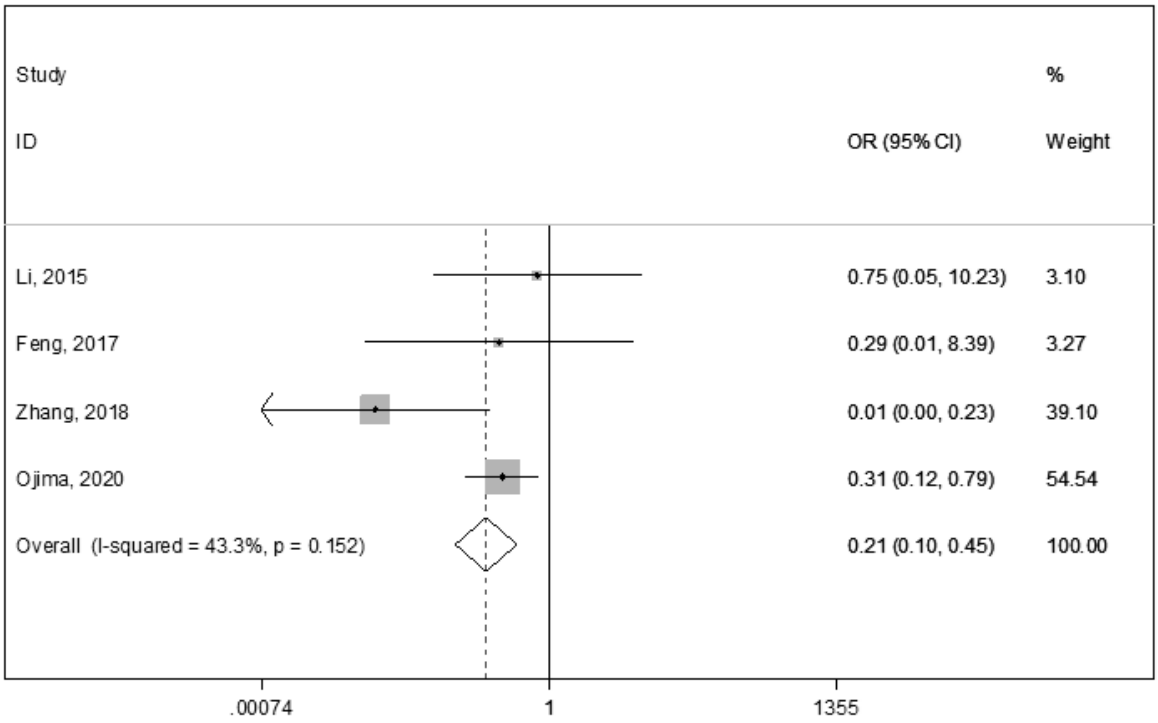

Figure 8

Comparison of complications rate for ESTD vs. ESD in gastric lesions.

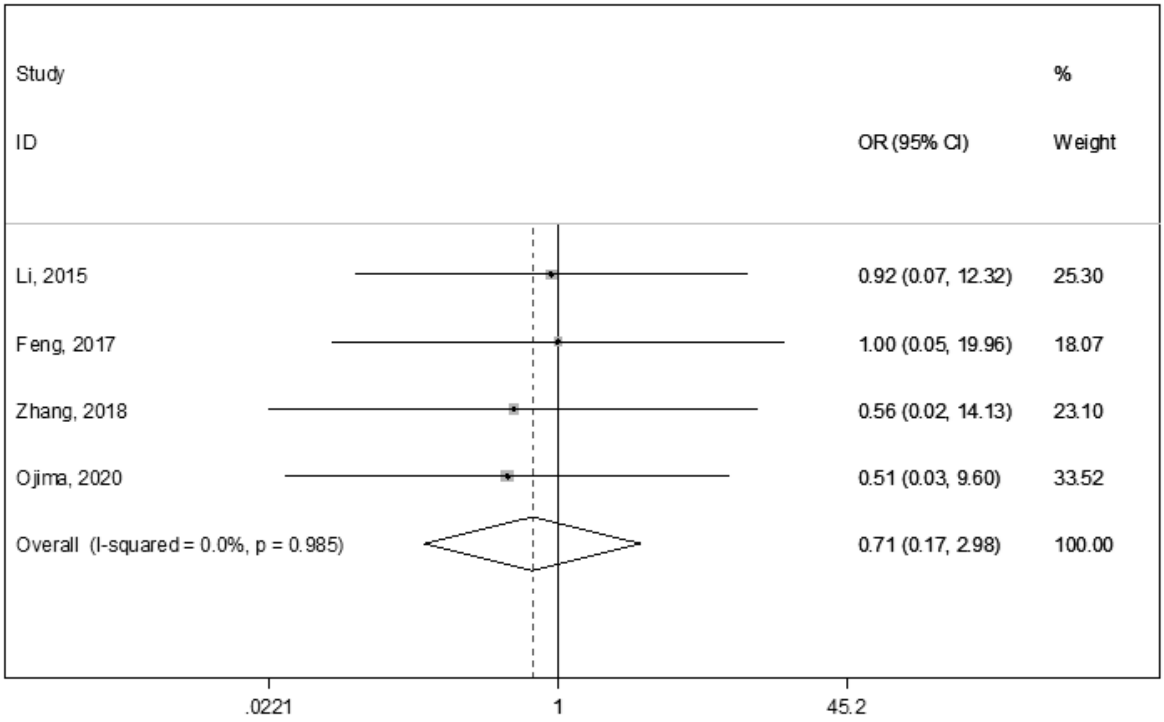

Figure 9

Comparison of recurrence rate for ESTD vs. ESD in gastric lesions.

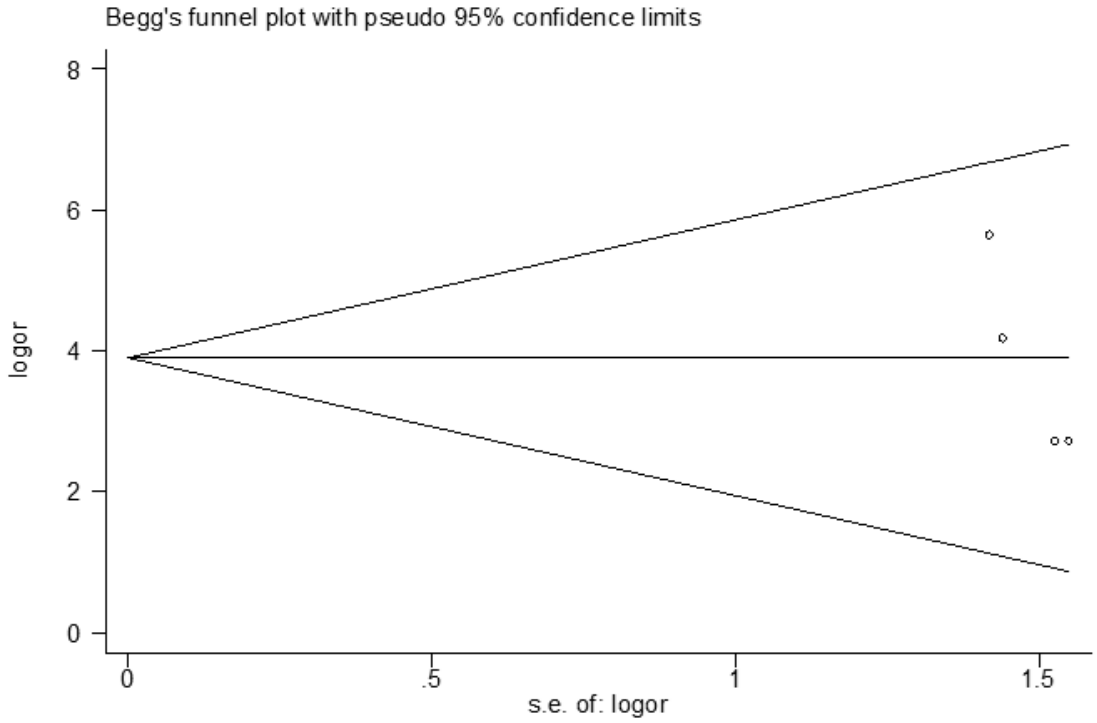

Figure 10

Funnel plot for publication bias of en bloc resection rate between ESTD and ESD for gastric lesions.